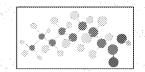




# RISK ASSESSMENT OF CHRONIC DRINKING WATER EXPOSURE TO PERFLUORONONANOIC ACID (PFNA

Gloria B. Post, New Jersey Department of Environmental Protection and Jessie A. Gleason, New Jersey Department of Health





## ABSTRACT

rfluorononanoic acid (PFNA) is detected in New Jersey drinking water more frequently and at higher concentrations ian elsewhere in the U.S. Available information suggests that PFNA is excreted more slowly and causes toxicity at lower ses than the closely related compound, perfluorooctanoic acid (PFOA). A draft drinking water concentration protective or chronic exposure to PFNA was developed. Review of 44 epidemiology studies found the strongest evidence for sociations with PFNA for serum cholesterol and the liver enzyme ALT. Effects seen in rodent studies include <u>velopmental effects, and liver, kidney immune system, and male reproductive system toxicity. A scrum level BMDL</u> 4900 ng/mi was developed for increased liver weight in pregnant mice. Uncertainty factors were applied, based on PA guidance, to develop a target human serum level, analogous to a Reference Dose, of 4.9 ng/ml. A chemical-speci elative Source Contribution factor of 0.5 was derived from NHANES data on 95" percentile exposures in the U.S. gener pulation. Based on the previously established serum drinking water rano of 100:1 for PFOA and relative half-lives of FOA and PENA in humans and animals, a serum drinking water ratio of 200.1 was estimated for PENA. The resulting dra hronic drinking water concentration is 0.013 µg/L (13 ng/L)

## BACKSROUND INBORRYATION

- in component (Child Suffor Sul

NA (£9)	3.0	3/122	2.5%	6/3483	0.2%
***********	************				



**************************************		8805	613	5.83-6.82	5.51	Τ
	0	3/8-0:A	2.03	3.95-2.42	2.08	t
		2 CEC (2+)				8
1 mm 1 m				To	sicokinet	::
		* Notin	etabolited	- chemically n	on-reactive	

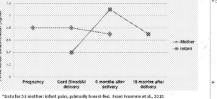


## Half-lives of PFNA and PFOA in Male and Female Mice and Rats (days)

	25	No.	2	50A	85886 5 <sub>12</sub> 5	: 5504 866:
	Wale	Egmple	5166	Sencie	adole.	Service
A::	30.6729.62	2.87/2.62	4.61	0.08-0.17	5.0-2.5	8,2-30
64cuse	34.37/98.4°	25.8768 9	19 <sup>4</sup>	22"	2.04.0	1.4-2.5

- Prematai exposum via maternal fetai transfer.
- Stadian cord blood serum-material serum ortio 19.5.

- maternal distraing water source; this relationship is not known for 04MA from illustrate invadants a



## Estimated Half-lives of PFNA and PFOA in Humans (years)

BIOMONITORING AND TOXICOKINETICS

Human Blomenitoring

Central rendency value (medium, mean, or geometric mean) 25% serum.

concentration ranged from 6.3 to 2.4 na/ms in human health studies of the

PPC Serum Concentrations (ng/mL) for the U.S. Population

Confidence Intervals 1.75 75% 50% 95%

cat states to an in the fact

Toxicokinetics

Strangtfeeding and menotional blood loss are add/Menal poster?

. Excreted slowly in humans (years), mais & female mice, and male rats

. William traffill the stroffer trasped on declare in specim terrals - not praffishly

United information from less definitive unitary excretion data.

Setembel Fermeraltes

4> 12 years of age) from NHANES 2011-2012\*

Eletarded in place sarum of 289% of U.S. general appulation.

general considerant from the IEE and other cofficer

· Also found to human breast milk and seminal fluid.

Gizametror Missan (95%)

· Distributed orimarily to serum. Ever and kidney.

Amounth six excretaed napid/s in female catalities six

9 9904 alon those this species/gender come

Alines to emtelos in these rissues.

Excepted to solve and feren

Concentrations are lower time for other vision cons 900.

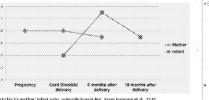
n decline in vels n urinary n, with d al	PFNA  No in formall males and females >50 years:	mation females 21-50 years:	PFOA  2.3-10.1ª/3. all males and females >50 years:	8 <sup>b</sup> years females 21-50 years:	and	females 21-50 years:	Concentration  • For PFCA, ratio of 2,10th between serum level and drinking water (all oncycing encourse) is well established.  • Available enlowed and frumen data support frumen halblife for PFNA at least take that of PFNA.  • Britished serum officing water ratio for PFNA of 100th is reasonable and over the property of the property
<50 years Mean		2.5	2.6		••••••	1.19	
tric Mean	3.2	1.7	1.2	1.5	2.67	1.13	
Median	3.5	1.5	1.7	1.8	2.06	0.83	

## \*Multiple studies of communities with dirinking water exposure reviewed in Post et al. (2012) - \*Oison et a (2007) - retired workers, "Zhang et al. (2013) - Chinese general population

25	No.	,	50A	25.68 5,5	: FFCA 866:
Make	Fernale	515%	Servaie	2656e	Servale
30.6729.67	2.87/2.62	4.61	0.08-0.17	5.0-2.5	8.2-30
34.3 <sup>4</sup> /98.4°	25.8768 9	19"	320	2,04.0	1.4 - 6

## Developmental Exposures

- · Infant exposure via breast milk and/or formula prepared with contaminated drimling water.
- Serum teseis increase during represtal period.
- infants consume more fluid on body weight basis than older
- For PFOA, concentration in breast milk is similar or higher than it



# Relationship between Orinking Water Exposure and Serum

- anathing experience is well established Available animal and turnsh data support human half-life for PFNA at least twice that of PPCA.
- Estimated varuna trinking water ratio for PFNA of 2000 is reasonable and not overly stringent.

l	25	Sat	2	50A		: FFOA Bode
1	Make	Female	5166	Female	aligie	Serroie
	30.6729.6	2.47/2.42	4.6	0.08-0.17	5.0-2.5	8.2-30
	54.3 <sup>5</sup> 758.4°	25.8768 9	19 <sup>4</sup>	37"	2.0-4.0	1.4-2.5

- 44 studies reviewed
- \* General population, 43 studies from U.S., Canada, Europe, and Asia

http://www.do

- Based on Work history
- Serum levels not provided
- Serum Bolds

- Remarked the numbers
- Other nutrimes Studies are primarily cross-sectional and cannot prove causality due to their design
- Consistant with most PFOA and PFOS studies
- Promovinamos veedovosi straty decier
- No evidence for association. Environd harming ear
- Distabase for many applicators is limited to one or a few studies

## Importance of PFNA Serum Levels in Toxicology Studie

- \* Large differences in half-lives between humans (several years) and codents (days to Much higher serum level in humans versus rodents from same external dose
- Occapitative human \*\*\* markent romnarism hased on senim levels foot axterna

## **HEALTH EFFECTS**

# Literature Search 20.000.000.000

## Human Epidemiology

- Analysis have ton reman lessets
- PEVA expensity correlates with other PEOs in servin.
- Veste di denograpio 9
- is the studies of fields convert monaturities beliefly there with decides water 85005078.
- r Endopints that were evaluated include:
- \* Metabolic parameters
- \* immune catero outcomes Thyroid harmones and related outcome
- se. Marienhaloscines; nutramas
- Discreta yourses and billion?
- Contribute to hazard identification, but not used as hasis for quantistive de- Evidence for associations strongest for serum cholesterol and the liver enzyme Al
- Minimal evidence of associations for other endpoints

- Shades that do not provide serum levels contribute to hazard identification? qualitative avaluation

1 acute inhalation study in rats.

## Animal Texicology

- a 10 short-term (1d day) projettidisci
  - \* 7 in male rats
  - \* 2 in male mice
- # 1 in mais & female mins 4 oral reproductive/developmental studies
  - \* 1 two-sensormon study in rate (Surface S-111)?
  - \* 3 gestaffonal exposure CO-1 reine
  - Wild-type and PPAS-sinks knockout (ICO) mos Rats
- . 1 Oral subchronic study (Surfam 5-513)\* in rats
- Generally rauses similar effects as PEGA but at lower doses.
- More circuity everated than \$500. \* Greater intrinsic potency than PFOA.
- \* Toxicological effects include

Chronic toxicity/cardinosenicity has not been studied

- Weight loss
- Even enlargement, wich accopic changes including inacrosis
- \* Kidney: enlargement, microscopic changes \* immune system (spleen & thymus); atrophy and changes in immune cell
- populations \* Testes imicrospopic changes and other effects
- \* Reproductive: decreased pregnancy rate, maternal weight loss, full litter recorpioss Offsoring: wortality, decreased weight eain persisting into adulthood.
- delays to reaching developmental milestones
- \*Toxicity of the PEC mixture, Surfan 3-111, is tikely primarily due to PENA.

## Comparison of developmental delays from PFNA and 2222 in CG 1 min

	FFUM III L	D=7 111105		- 3
	E-E	NA	PEGA	11 8
Endpoint	(Das et a	d., 2015)	(Lau et al., 2006)	
	3 mg/kg/day	5 mg/kg/day	20 mg/kg/day	
ye opening	2 days	5 days	~3 days	1
aginal opening	3 days	7 days	13 days	]
reputtal Separation	2 days	5 days	173. day	11 8

## Mode of Action

- Not considered to be genotoxic
- Activates receptors found in many tissues that regulate expression of genes related to campaganicity Ever revisity Enid matabolism days normantal toxicity immunotoxicity and other effects. Most potent in vitro activator of human and mouse peroxisome.
- proliferator activated receptor-o (PFAR-e) in sense of perfluorocarpoxylates with 4 to 32 carbons. Over toxicity has both 29A8- or dependent and 29A8- or independent
- Specific toxicological machanisms suggested for: Effects on liver, immune system, male reproductive system, elucase and

# Conduction: Effects of PFM4 in molecus are considered relevant to humans

## DEVELOPMENT OF CHRONIC DRINKING WATER CONCENTRATIO

Target Human Serum Level

Concentrating Factors (CFR) appoins to Found of Department Total = 1900.

Relative Source Contribution (RSC)

Intended to prevent total exposure from expecting Reference Date (or

\* Less stringent chamical specific RSC it sufficient information

"Subtraction injurialist" based on 95° percentile 20%4 servin levels.

Refrection S.S. Nacragoround expressions does to tone, which exist, written and in

Targat human serum level – 95<sup>th</sup> NHANES terum level — <sub>X 300</sub>

4.9 ng/mi - 2.5 ng/mi x 100

RSC ~ 49 % = 56.0% or 6.5

Continue to hardeling reset partition in within a spectical

ES<sup>®</sup> percentile - protective of nun-drinking water exposurer.

Anxiograph to Referency Cross but on secure legal basis.

3: Animal Automorphism to Indicate a mile of Merenias;

After Signature than enqually recognized as exposure

4900 na/mi - 4.9 signo er 4909 agit.

3: incommete todomosichi ditapise.

Cuidance provided by USERA (2000)

Range of potential RSCs: 2014 to 30%.

tanget human serum levels.

292 200

consumer products

from most recent NHANES.

## Evaluation by Other Government Agencies Benchmark Dose (BMD) Modeling

support in congruent mine or or 196 ordinario

model (4.43 µg/ml).

in 166 Marson (caranto)

- No reach deservative have been developed by other government abond as 1940 more for 67 MA section level gravitating with 10% original or the
- European Chemical Aseans (ECHA) classification (2014)
- Ut seven made's run. Hill model and Exponential 5 model, both had A Characterial to mate with advisorable topicant a function to contain that lowest AIC statistic (-15.5) and exhalient fit.
- \* Suspected human reproductive taxicant ferfility Point of Departure for risk assessment is 4.9 µg/ml (4990 ng/ml) Suspected human sercinogen. \* Average of SMOLs from Hill mode (0.43 ug/m) and Exponential 5
- Target organ toxiciny after prolonged or repeated exposure -fives; Shamon inten

## Weight of Evidence for Carcinogenicity

Having to breast 4x6 child through effects on or yet actation.

 No information on care mogenitaty. Bink at exercision has an execution or attents

to U.S. or elsewhere.

- Key and Supporting Studies and Endpoints
- Yay Study, Das et al. (3015) study at developmental attacts in mice.
- Sev Endpoint increased material (her weight in pregnant mate). 4. Serum levels and over weights measured at 60 17 tone day after test.
- Remounerarkeut trumpsame
- \* USASU 1 ma/us/on
- No.8042: Sextiller Model accepted had tradecimental adjust of PERM
- Simple date response for PPNA serum levels and increased liver weight make mine followers at all 1951 dis-
- Chose affects of single on power administered doses in same angles and taxioniaxionintudies: 71 Laws memory (at those lower than those causing increased like
- 998(801) Security among the force in the large day specification of the environment of the contraction. adulthond
- to remune system toxicity Make reproductive system feeticity
- Homen and annihology of other Americations deserted in general nepolation provide supporting evidence but not used as basic for quantitative mix.

## Serum: Drinking Water Ratio

- Estimated RENA serum providing water ratio 200 to
- Used to relate serious level to dismong water concentration or consideration of health-bases of his or water.

- Target Ruman Serum Level 4 4.9 ng/millor 4900 ng/k 980s 80% and 8

or 200 ng/L in serum per ng/L in dimiling water.

Uncertainties

Sepum: difinking water ratio = 200:1

- Ongoing exposure to 13 par A Estimated 3 told increase in general population service concentrations.
- Attraction of the property of the property of the cold of the least one. out for eventure
- Prefincient called constructed and potentially more security. \* Debet RSC of 10% when insofficient character specific information nut used at basis hecapte serum PFNA dath not available
  - andopiere a 18198 has not been etiletier for come loss done - Appellopments Leffecti copred to MIGA in an imals.
  - 200 1 renum drinking water raths consulated reasonable Chine: PCC: have similar toxic effects and mode of ention.

Destantial for ambition territory arts who a 970 for that more two present in dirinking water not considered.

- Remisesante a formesi front consur memantital painu.
- ranzeztzikan

ali Program di Salam di Salam di Salam

- Bolleon 18 Herris C.C. Stort Co. L. Dept. 141 Herris Co. D. Deven

- No chronic toxicology studies of concentral other.

# For More Information

insent is posted at the Au-Drinking material sills in titue wersite a

# ED 002330 00119332-0000